wherein R^1 to R^5 are as defined in claim 2, R^6 is hydrogen or optionally protected hydroxy; R^7 is alkoxy, optionally protected hydroxy, oxo or optionally O-substituted oxyimino; and R^8 is hydrogen, optionally protected hydroxy, or a group 4′-(a-L-oleandrosyl)-a-L-oleandrosyloxy or a-L-oleandrosyloxy wherein the terminal hydroxy group is optionally protected; wherein any two of R^2 to R^5 may be taken together with the carbon atom(s) to which they are attached to form cycloalkyl, aycloalkenyl, aryl or heterocyclyl group.

Please add new claims 6 and 7 as follows:

6. (NEW) A pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milemycin, in the form of a complex with at least one cyclodextrin; wherein said anthelmintically active compounds is 5-oximino-22, 23-dihydro-25-cyclohexylavermectin B1 monosaccharide.

7. (NEW) The pharmaceutical composition of claim 6, wherein the cyclodextrin is a-, b- or g-cyclodextrin, or a derivative or mixture thereof.

REMARKS

Claims 1-5 were pending in the present application. Claims 2 and 3 are amended and new claims 6 and 7 are added. Support for the amendments to claim 2 can be found, *inter alia*, on page 3, lines 1-4 and page 4, lines 15-17 of the original specification. Support for the amendments to claim 3 can be found, *inter alia*, on page 4, lines 15-17. Support for new claims 6 and 7 can be found, *inter alia*, in the original claims 7 and 8, respectively. Therefore, the amendments are fully supported by the original specification and do not raise any issue of new matter. Accordingly, entry of the present Amendment is respectfully requested. Upon entry of the present Amendment, claims 1-7 will be under examination.

CLAIM REJECTION UNDER 35 U.S.C. §112

Claims 2-5 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action objects to the use of the phrase "an organic radical."

Applicants respectfully point out that claim 2 is amended to clarify that the "organic radical" is "selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclic, mono-, bi- and tri-cycloalkyl, mono-, bi- and tri-cycloalkenyl and aralkyl, or any two of R^2 to R^5 may be taken together with the carbon atom(s) to which they are attached to form cycloalkyl, aycloalkenyl, aryl or heterocyclyl group." Applicants contend that the use of this

phrase in the amended claim 2 clearly defines the metes and bounds of the claimed subject matter as one of ordinary skill in the art would understand what is claimed, in light of the specification." see MPEP 2133.05(b). Therefore, reconsideration and withdrawal of this rejection are respectfully requested.

CLAIM REJECTION UNDER 35 U.S.C. §103(a)

Claims 1-5 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Loftsson, U.S. Patent No. 5,472,954 ("Loftsson") in combination with Asato, U.S. Patent No. 4,886,829 ("Asato"). However, the Office Action acknowledges that "Asato does not teach the combination of the anthelmintic compound with cyclodextrin" and "Loftsson does not specifically teach the use of the compound of formula I with a cyclodextrin." *Office Action at page 3*. The Office Action asserts that "one of ordinary skill in the art would have been motivated to combine an anthelmintic with a cyclodextrin for the purpose of obtaining a complex with improved water solubility over the uncomplexed drug while maintaining the biological activity of said drug." *Office Action at page 4*.

In order to expedite the prosecution of the present application, without conceding to the correctness of the Office Action's position, Applicants have amended claim 2 to clarify that the "organic radical" is "selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heterocyclic, mono-, bi- and tri-cycloalkyl, mono-, bi- and tri-cycloalkenyl and aralkyl." Applicants have also amended claim 3 to emphasize that the complex is formed between at least one cyclodextrin and the compound of formula (I).

Applicants respectfully point out that the Office Action fails to establish a *prime facie* case of obviousness under the standard of M.P.E.P. § 2142 which states that:

> to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

The Office Action does not meet at least the first and third requirements. Specifically, Loftsson discloses a method for enhancing the complexation of a cyclodextrin with lipophilic and/or water-labile active ingredient with the addition of a water soluble polymer. Asato

discloses 23-oxo (keto) and 23-imino derivatives of certain C(26, 27)-epoxy- and C(14, 15; 26, 27)-diepoxy-LL-F28249 compounds. Applicants respectfully point out that there is no teaching or suggestion that Loftsson and Asato can be combined. Even if these two references can be combined, the Loftsson-Asato combination does not provide any specific teaching, suggestion or motivation to a skilled artisan on how to obtain the claimed pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milbemycin, in the form of a complex with at least one cyclodextrin. Nor does the Loftsson-Asato combination provide any teaching or suggestion on the use of the compound of formula I with a cyclodextrin.

Moreover, without looking at the disclosure of the present application, one of ordinary skill in the art would not know from Loftsson-Asato combination how to obtain the claimed pharmaceutical composition having the advantages described in the specification, e.g. the degradation rate of the anthelmintically active compound in the complex is much slower than uncomplexed compound. In fact, page 9 of the original specification shows that after storing at 50^0C for eight weeks, 5% of the milbemycin in the milbemycin complex degraded while 54.3% of the uncomplexed milbemycin degraded under the same conditions. Therefore, the Office Action does not satisfy the first criteria for establishing a *prime facie* case of obviousness under M.P.E.P. § 2143.01 because the "suggestion or motivation" criteria must be satisfied from the disclosure of the prior art reference or from the knowledge of persons skilled in the art, not by the use of hindsight in view of the present application (emphasis added).

In this case, the Loftsson-Asato combination does not disclose "all the claim limitations." Specifically, Loftsson-Asato combination does not disclose the pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milbemycin, in the form of a complex with at least one cyclodextrin, having the advantages, such as low degradation rate, as described in the specification. Nor does the Loftsson-Asato combination disclose the use of the compound of formula I with a cyclodextrin as defines in claim 3, as amended. In fact, the Office Action acknowledged that "Loftsson does not specifically teach the use of the compound of formula I with a cyclodextrin" and "Asato does not teach the combination of the anthelmintic compound with cyclodextrin." Therefore, the Office Action fails to satisfy the third criteria for establishing a *prime facie* case of obviousness under the M.P.E.P. § 2143.01.

Furthermore, Applicants have achieved unexpectedly superior results in the form of a ten-fold reduction in the rate of degradation of the anthelmintically active compound in the claimed composition. Specifically, page 9 of the original specification shows that the formation of milbemycin-cyclodextrin complex reduces milbemycin degradation from 54.3% to 5% after storing at 50^0C for eight weeks. Such superior property of the claimed composition is evidence of nonobviousness under M.P.E.P. §716.02(a).

In addition, M.P.E.P. §2144.04(II)(B) states that "the omission of an element and retention of its function is an indicia of unobviousness." In this case, Loftsson disclosed that one desirable component of its composition is a pharmacologically inactive water-soluble polymer which enhances the complexation of a cyclodextrin with a lipophilic and/or water labile active ingredient. The pending claims of the present application do not include such a pharmacologically inactive water-soluble polymer. Therefore, even assuming that the composition from Loftsson-Asato combination also achieved slow degradation of the lipophilic and/or water labile active ingredient, the pending claims would still be nonobvious over the Loftsson-Asato combination under the standard of M.P.E.P. §2144.04(II)(B) as the claimed composition does not include "a pharmacologically inactive water-soluble polymer." Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

CONCLUSION

In view of the claim amendments and the remarks, Applicants believe that present Amendment addresses all outstanding issues of the Office Action. Further and favorable consideration of the present application and the issuance of a Notice of Allowance with regard to all pending claims are respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Date: March 31, 2003

Lance Y. Liu
Attorney for Applicants
Reg. No. 45,379

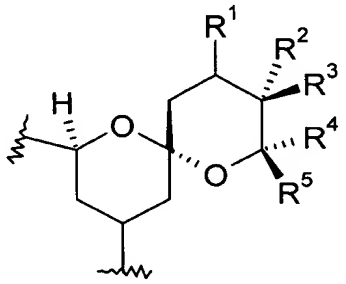
Pfizer Inc
Patent Department
Eastern Point Road, MS 8260-1611
Groton, Connecticut 06340
(860) 686-1652

Customer ID: 28523

Version with Markings to Show Changes Made

IN THE CLAIMS:

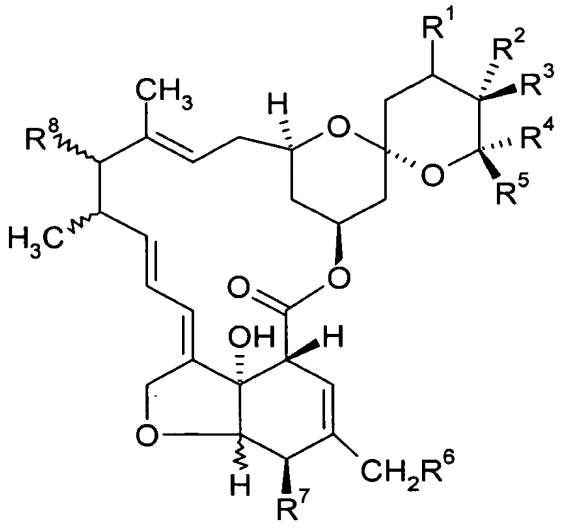
2. A composition as claim in Claim 1 in which the avermectin or milbemycin is milbemycin, ivermectin, doramectin, moxidectin, nemadectin, abamectin or a compound of the partial formula (i)



(i)

wherein R^1 is an optionally substituted amino or imino group, such as optionally O-substituted oxyimino, optionally N-substituted hydrazone or optionally N-substituted semicarbazone, and R^2 to R^5 are the same or different and each is hydrogen or an organic radical which is selected from the group consisting of alkyl, akenyl, alkynyl, aryl, heterocyclic, mono-, bi- and tri-cycloalkyl, mono-, bi- and tri-cycloalkenyl and aralkyl, or any two of R^2 to R^5 may be taken together with the carbon atom(s) to which they are attached to form cycloalkyl, aycloalkenyl, aryl or heterocyclyl group.

3. A pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milemycin, in the form of a complex with at least one cyclodextrin; wherein said anthelmintically active compound is represented by ~~A composition as claimed in claim 2 in which the compounds of formula (i) are compounds of~~ formula (I):



(I)

wherein R^1 to R^5 are as defined in claim 2, R^6 is hydrogen or optionally protected hydroxy; R^7 is alkoxy, optionally protected hydroxy, oxo or optionally O-substituted oxyimino; and R^8 is hydrogen, optionally protected hydroxy, or a group 4′-(a-L-oleandrosyl)-a-L-oleandrosyloxy or a-L-oleandrosyloxy wherein the terminal hydroxy group is optionally protected; wherein any two of R^2 to R^5 may be taken together with the carbon atom(s) to which they are attached to form cycloalkyl, aycloalkenyl, aryl or heterocyclyl group.

6. A pharmaceutical composition comprising at least one anthelmintically active compound which is an avermectin or milemycin, in the form of a complex with at least one cyclodextrin; wherein said anthelmintically active compounds is 5-oximino-22, 23-dihydro-25-cyclohexylavermectin B1 monosaccharide.

7. The pharmaceutical composition of claim 6, wherein the cyclodextrin is a-, b- or g-cyclodextrin, or a derivative or mixture thereof.